PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
469201-519		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US01/02618	26/01/2001	27/01/2000
International Patent Classification (IPC) or national classification and IPC C07K16/10		
Applicant MEDIMMUNE, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/08/2001	10.04.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Renggli, J Telephone No. +49 89 2399 7461

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US01/02618

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-44	as originally filed				

Claims, No.:

1-16	as originally filed				
17-46	as received on	29/03/2001	with letter of	27/03/2001	

Drawings, sheets:

1/10-10/10	as originally filed

Sequence listing part of the description, pages:

1-11, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☒ furnished subsequently to this Authority in computer readable form.
   ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☒ The statement that the information recorded in computer readable form is identical to the written sequence

listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 34-36,44-46 with respect to industrial applicability.

because:

   ☒ the said international application, or the said claims Nos. 34-36,44-46 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,8,10,14-27,36,42,43,46
	No:	Claims	1-6,9,11-13,28-35,37-41,44,45
Inventive step (IS)	Yes:	Claims	18-27
	No:	Claims	1-17,28-46
Industrial applicability (IA)	Yes:	Claims	1-33,37-43
	No:	Claims	

2. Citations and explanations
see separate sheet

ITEM III:

Claims 34-36 and 44-46 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

ITEM V:

1. Reference is made to the following documents:

D1 YANG W -P ET AL, JOURNAL OF MOLECULAR BIOLOGY, vol. 254, 1995, pages 392-403, XP000199739
D2 EGAN ROBERT W ET AL, ARZNEIMITTEL-FORSCHUNG, vol. 49, no. 9, 1999, pages 779-790, XP000999038
D3 WO 99 28471 A
D4 US-A-5 929 212
D5 LOVE ROBERT A ET AL, BIOCHEMISTRY, vol. 32, no. 41, 1993, pages 10950-10959, XP000999742
D6 WHITLOW MARC ET AL, PROTEIN ENGINEERING, vol. 8, no. 8, 1995, pages 749-761, XP000999039
D7 WO 96 05229 A
D8 BALINT R F ET AL, GENE, vol. 137, no. 1, 27 December 1993 (1993-12-27), pages 109-118, XP002031537 ISSN: 0378-1119

2. Industrial applicability (Art. 33(4) PCT):

The subject-matter of claims 1-33 and 37-43 is susceptible of industrial application.

For the assessment of the present claims 34-36 and 44-46 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a

known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Novelty (Art. 33(2) PCT):

D1 concerns high affinity human anti-HIV-1 human Fab antibodies, made by CDR mutagenesis. One of the antibody has a Kd of 15 pM. These antibodies may be used for passive immunization against HIV (see D1, abstract; Table 5; Discussion).
D1 anticipates the subject-matter of claims 1-6, 9, 11, 28-35, 37-41, 44 and 45 of the present application.

D2 is directed to a humanized antibody against human IL-5 with a Kd of 20 pmol/l. The consensus region of human IgG4 were used as framework. The antibody was tested in vivo in mice and prevented the influx of eosinophils. The antibody may be used in humans against IL_5 related diseases like asthma (see D2, abstract).
D2 anticipates the subject-matter of claims 1-5, 9, 11-13, 28-32, 34, 37-40 and 44 of the present application.

D3 discloses anti mesothelin antibodies with a Ka of 10^{-10} (see D3, claims; example 4; page 21, line 22-page 22, line 9).
D3 anticipates the subject-matter of claims 1-5, 9, 11-13, 28-32, 34, 37-40 and 44 of the present application.

D4 discloses humanized anti-CD3 antibodies having an affinity 10^{-8}-10^{-12} which may be used therapeutically (see D4, column 1, lines 8-28; c. 6, lines 34-44; c. 7, lines 8-11; figure 12, claims).
D4 anticipates the subject-matter of claims 1-5, 9, 11-13, 28-32, 34, 37-40 and 44 of the present application.

D5 concerns a murine monoclonal antibody with a Ka of 1.1×10^{10} M-1 for its antigen, a metal chelate called In-EOTUBE. A corresponding Fab' fragment was constructed. The antibody may be used as an imaging agent in vivo (see D5, abstract and introduction).
D5 anticipates the subject-matter of claims 1-4, 12, 13, 32 and 37-40 of the present application.

D6 describes an anti-fluorescein Fab with a Ka of 10^{10} M^{-1}. Also disclosed are a single - chain Fv counterpart and the parent antibodies (see D6, abstract; figs. 3-5; material and methods).
D6 anticipates the subject-matter of claims 1-4, 12, 13 and 37-40 of the present application.

4. Inventive step (Art. 33(3) PCT):

The additional features contained in claims 7, 8, 10, 14-27, 36, 42, 43 and 46 render the said claims novel over D1-D6.

The said claims are also novel over D7 which discloses anti-RSV antibodies which do not have a K_a of at least 10^{10} M^{-1} (see D7, whole document).

At this stage, it is noted that the present application discloses high affinity antibody against the F antigen of RSV (see p. 27, lines 24-27). All of the said antibodies contain at least 4 modified CDRs, namely H1, H3, L2 and L3 (see also figures 2, 8 and 9 and page 34, line 25-page 36, line 12 of the present application).

It is not clear where in the description experiments have been made to ascertain that the incorporation of only three, two or a single modified CDR as claimed in claims 7, 8, 10, 14, 15, 16, 17, 36, 42, 43 and 46 can lead to the provision of a high affinity antibody against the F antigen of RSV, let alone against any other antigen. It is here noted that the generation of antibodies having a very high affinity (pM range) is generally considered to be a difficult task (see D8, page 110, right-hand column).
The said claims do not thus appear to be inventive within the meaning of Article 33(3) PCT, as it has not been demonstrated that the replacement of one to three CDRs only enables the provision of high affinity antibodies as defined in claim 1

Concerning claims 18-27, it is noted that these antibodies have a high affinity against the F antigen of RSV (see pages 34-36 and figs. 3-7; page 40, Table 4) and all contain at least 4 modified CDRs.

The problem to be solved over the closest prior art document D7 can thus be seen as the provision of high affinity antibodies, potentially useful against RSV.

The solutions consist in the modified CDRs and/or the related seq IDs indicated in claims 18-27.

The solution cannot be derived in an obvious way from the cited prior art and claims 18-27 are thus considered to be inventive.

17. The high affinity neutralizing immunoglobulin of claim 1 wherein said immunoglobulin has a high affinity L3 CDR having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 15 and 16.

18. The high affinity neutralizing immunoglobulin of claim 1 wherein the H1 CDR has the amino acid sequence of SEQ ID NO: 9, the H3 CDR has the amino acid sequence of SEQ ID NO: 11, the L2 CDR has the amino acid sequence of SEQ ID NO: 4 and the L3 CDR has the amino acid sequence of SEQ ID NO: 14.

19. The high affinity neutralizing immunoglobulin of claim 1 wherein the H1 CDR has the amino acid sequence of SEQ ID NO: 9, the H3 CDR has the amino acid sequence of SEQ ID NO: 11, the L2 CDR has the amino acid sequence of SEQ ID NO: 12 and the L3 CDR has the amino acid sequence of SEQ ID NO: 5.

20. The high affinity neutralizing immunoglobulin of claim 2 wherein the H1 CDR has the amino acid sequence of SEQ ID NO: 10, the H3 CDR has the amino acid sequence of SEQ ID NO: 11, the L2 CDR has the amino acid sequence of SEQ ID NO: 12 and the L3 CDR has the amino acid sequence of SEQ ID NO: 14.

21. The high affinity neutralizing immunoglobulin of claim 2 wherein the H1 CDR has the amino acid sequence of SEQ ID NO: 9, the H3 CDR has the amino acid sequence of SEQ ID NO: 11, the L2 CDR has the amino acid sequence of SEQ ID NO: 12 and the L3 CDR has the amino acid sequence of SEQ ID NO: 14.

22. The high affinity neutralizing immunoglobulin of claim 2 wherein the H1 CDR has the amino acid sequence of SEQ ID NO: 9, the H3 CDR has the amino acid sequence of SEQ ID NO: 11, the L2 CDR has the amino acid

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sequence of SEQ ID NO: 12 and the L3 CDR has the amino acid sequence of SEQ ID NO: 15.

23. The high affinity neutralizing immunoglobulin of claim 1 wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 17 and the heavy chain variable region has the amino acid sequence of SEQ ID NO: 18.

24. The high affinity neutralizing immunoglobulin of claim 1 wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 19 and the heavy chain variable region has the amino acid sequence of SEQ ID NO: 20.

25. The high affinity neutralizing immunoglobulin of claim 2 wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 21 and the heavy chain variable region has the amino acid sequence of SEQ ID NO: 22.

26. The high affinity neutralizing immunoglobulin of claim 2 wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 23 and the heavy chain variable region has the amino acid sequence of SEQ ID NO: 24.

27. The high affinity neutralizing immunoglobulin of claim 2 wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 25 and the heavy chain variable region has the amino acid sequence of SEQ ID NO: 26.

28. A recombinant high affinity neutralizing immunoglobulin having an affinity constant of at least 10^{10} M^{-1}, wherein said immunoglobulin comprises a human constant region and a heavy and light chain framework region at least part of which is derived from human antibodies.

29. The recombinant high affinity neutralizing immunoglobulin of claim 30 wherein the heavy and light chain framework regions are derived from a consensus sequence of human antibodies.

30. The recombinant high affinity neutralizing immunoglobulin of claim 30 wherein the affinity constant is at least 10^{11} M^{-1}.

31. The recombinant immunoglobulin of claim 30 wherein the heavy and light chain framework regions are derived from a consensus sequence of human antibodies.

32. A composition comprising the immunoglobulin of claim 1 wherein said immunoglobulin is suspended in a pharmacologically acceptable carrier.

33. A composition comprising the immunoglobulin of claim 6 wherein said immunoglobulin is suspended in a pharmacologically acceptable carrier.

34. A method of preventing and/or treating a disease comprising administering to a patient at risk thereof, or afflicted therewith, a therapeutically effective amount of the immunoglobulin composition of claim 32.

35. A method of preventing and/or treating a virus-induced disease comprising administering to a patient at risk thereof, or afflicted therewith, a therapeutically effective amount of the immunoglobulin composition of claim 33.

36. A method of preventing and/or treating respiratory syncytial virus comprising administering to a patient at risk thereof, or afflicted therewith, a therapeutically effective amount of the immunoglobulin of claim 7 suspended in a pharmaceutically acceptable carrier.

37. The high affinity neutralizing immunoglobulin of claim 3 wherein said immunoglobulin is selected from the group consisting of Fab, $F(ab)'_2$, a heavy-light chain dimer, a heavy chain and a light chain.

38. The high affinity neutralizing immunoglobulin of claim 4 wherein said immunoglobulin is selected from the group consisting of Fab, $F(ab)'_2$, a heavy-light chain dimer, a heavy chain and a light chain.

39. The high affinity neutralizing immunoglobulin of claim 1 wherein said immunoglobulin is an antibody.

40. The high affinity neutralizing immunoglobulin of claim 2 wherein said immunoglobulin is an antibody.

41. The high affinity neutralizing immunoglobulin of claim 6 wherein said immunoglobulin is selected from the group consisting of Fab, $F(ab)'_2$, a heavy-light chain dimer, a heavy chain and a light chain.

42. The high affinity neutralizing immunoglobulin of claim 7 wherein said immunoglobulin is selected from the group consisting of Fab, $F(ab)'_2$, a heavy-light chain dimer, a heavy chain and a light chain.

43. The high affinity neutralizing immunoglobulin of claim 8 wherein said immunoglobulin is selected from the group consisting of Fab, $F(ab)'_2$, a heavy-light chain dimer, a heavy chain and a light chain.

44. A method of preventing and/or treating a disease comprising administering to a patient at risk thereof, or afflicted therewith, a therapeutically effective amount of the immunoglobulin of claim 37 or 38 suspended in a pharmaceutically acceptable carrier.

45. A method of preventing and/or treating a virus-induced disease comprising administering to a patient at risk thereof, or afflicted therewith, a therapeutically effective amount of the immunoglobulin of claim 41 suspended in a pharmaceutically acceptable carrier.

46. A method of preventing and/or treating respiratory syncytial virus comprising administering to a patient at risk thereof, or afflicted therewith, a therapeutically effective amount of the immunoglobulin of claim 42 or 43 suspended in a pharmaceutically acceptable carrier.